

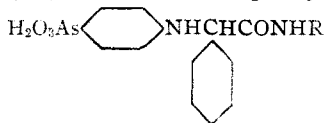
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MEDICAL RESEARCH.]

AROMATIC ARSENIC COMPOUNDS. VI. *N*-(PHENYL-4-ARSONIC ACID)- α -PHENYLGLYCINE AND ITS AMIDES.

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As a special extension of the general type of substances represented by the substituted amides, ureides and anilides of the phenylglycine arsonic acids,¹ *N*-(phenyl-4-arsonic acid)- α -phenylglycine,



its amide, ureide and a few of the substituted anilides were prepared and studied. With the exception of the glycine itself, which was obtained by hydrolysis of the amide, these substances were made from sodium arsanilate and the phenylchloroacetyl-amino compounds. It was necessary in every case to employ sodium iodide in 50% alcoholic solution in order to accelerate the condensation, since the chloro compounds alone showed little tendency to react.

The general properties of this group of substances resemble those of the simpler glycine derivatives.

Experimental.

N-(Phenyl-4-arsonic Acid)- α -phenylglycine, *p*-H₂O₃AsC₆H₄NHCH(C₆H₅)CO₂H.—Although this substance unquestionably could be prepared from arsanilic acid and α -phenylchloroacetic acid just as phenylglycine *p*-arsonic acid has been prepared, we have obtained it by hydrolysis of the corresponding amide described below, and which we had previously prepared.

30 g. of the sodium salt of *N*-(phenyl-4-arsonic acid)- α -phenylglycine-amide were dissolved in about 5 parts of 10% sodium hydroxide solution and boiled for about 15 minutes, after which the evolution of ammonia ceased. On adding hydrochloric acid to the chilled solution until acid to congo red the free arsonic acid separated as a colorless oil which rapidly crystallized. The compound was recrystallized from a large volume of boiling water, forming lustrous, rhombic plates. The yield was 20 g. When rapidly heated to 195°, then slowly, the acid darkens and sinters, and finally effervesces at 202–3°. It is sparingly soluble in the cold in water, alcohol or acetic acid, but dissolves more readily on warming. It is more easily soluble in methyl alcohol.

Subs., 0.2077 (Kjeldahl); 6.1 cc. 0.1 *N* HCl. Subs., 0.2674; Mg₂As₂O₇, 0.1168.

Calc. for C₁₄H₁₄O₅NAs: N, 3.99; As, 21.36. Found: N, 4.11; As, 21.10.

¹ THIS JOURNAL, 41, 1585 (1919).

N-(Phenyl-4-arsonic Acid)- α -phenylglycineamide, p -H₂O₃AsC₆H₄NH-CH(C₆H₅)CONH₂.—87 g. of arsanilic acid dissolved in 400 cc. of *N* sodium hydroxide solution, 80 g. of sodium iodide, 68 g. (1 mol.) of phenylchloroacetamide, and 500 cc. of alcohol were boiled for 4 hours. The mixture set to a solid cake on cooling. This was disintegrated and stirred with dil. hydrochloric acid until acid to congo red. The crude arsonic acid obtained in this way was purified through the sodium salt as described below. On dissolving a portion of this in water and adding acetic acid the free arsonic acid gradually separates as microscopic needles which do not melt below 280°. The substance is sparingly soluble in boiling water or 50% alcohol and practically insoluble in the cold.

Subs., 0.3260 (Kjeldahl); 19.05 cc. 0.1 *N* HCl. Subs., 0.3055; Mg₂As₂O₇, 0.1337.
Calc. for C₁₄H₁₅O₄N₂As: N, 8.00; As, 21.39. Found: N, 8.19; As, 21.12.

Sodium Salt.—The crude, washed acid was suspended in warm water, stirred, and treated with 50% sodium hydroxide solution until clear. After exactly neutralizing to litmus with acetic acid the warm solution was filtered, stirred, and treated with powdered sodium acetate until crystallization of the arsonate began. After standing in the ice-box overnight the salt was filtered off, washed first with 20% sodium acetate solution, then with alcohol, and finally recrystallized from alcohol, forming granular aggregates of plates. The yield of air-dried salt was 76 g., the amount of water of crystallization varying from 3.5 to 5 molecules in different preparations. The salt dissolves readily in water or boiling alcohol.

Prepn. 1: Subs., air-dry, 0.3384; loss, 0.0659 *in vacuo* at 100° over H₂SO₄.

Prepn. 2: Subs., 0.6091; loss, 0.0931.

Calc. for C₁₄H₁₄O₄N₂AsNa.3.5H₂O: H₂O, 14.48. For 5 H₂O: H₂O, 19.48.

Found: Prepn. 2: H₂O, 15.28. Prepn. 1: H₂O, 19.47.

1—Subs., anhydrous, 0.2592; (Kjeldahl) 13.80 cc. 0.1 *N* HCl.

2—Subs., anhydrous, 0.1577; 10.6 cc. N (25.5°, 758 mm.). Subs., 0.3242; Mg₂As₂O₇, 0.1335.

Calc. for C₁₄H₁₄O₄N₂AsNa: N, 7.53; As, 20.13. Found: N, 7.46, 7.67. As, 19.88.

N-(Phenyl-4-arsonic acid)- α -phenylglycineureide, p -H₂O₃AsC₆H₄NH-CH(C₆H₅)CONHCONH₂.—4.4 g. of arsanilic acid, 5.3 g. (1.25 mols) of phenylchloroacetyl-urea,¹ 4 g. of sodium iodide, 21 cc. of *N* sodium hydroxide solution, and 22 cc. of alcohol were boiled on the water bath for two hours. On cooling, acidifying to congo red, and rubbing, the glycineureide crystallized. The collected substance was purified by suspending in water, adding sodium hydroxide until faintly alkaline to litmus, filtering, diluting with hot water, and acidifying with acetic acid. The arsonic acid gradually separates in radiating masses of microscopic needles which contain one molecule of water of crystallization when air-dried. When rapidly heated the anhydrous substance swells and evolves

¹ THIS JOURNAL, 39, 2433 (1917).

gas at 195–7°. It is soluble in boiling water or 50% alcohol, but sparingly so in the cold. The yield was 3.5 g.

Subs., air-dry, 0.4267; loss, 0.0199, *in vacuo* at 100° over H₂SO₄.

Calc. for C₁₅H₁₆O₈N₃As.H₂O: H₂O, 4.38. Found: 4.66.

Subs. anhydrous, 0.3048 (Kjeldahl); 23.1 cc. 0.1 N HCl. Subs., 0.3045; Mg₂As₂O₇, 0.1196.

Calc. for C₁₅H₁₆O₈N₃As: N, 10.69; As, 19.06. Found: N, 10.62; As, 18.95.

N-(Phenyl-4-arsonic Acid)- α -phenylglycine-3'-hydroxylanilide, *p*-H₂O₃AsC₆H₄NHCH(C₆H₅)CONHC₆H₄OH(*m*).—10.5 g. of *m*-phenylchloroacetyl-aminophenol,¹ were employed as in the previous cases. The resulting purple solution was diluted with water and decanted from the gummy precipitate, which was digested on the water bath with hot water. As crystallization could not be induced the mixture was set aside for about a month, when crystals began to form. The process was accelerated by warming and stirring, and the crystals were finally filtered from the hot solution and washed with hot water. The dark purple product was recrystallized twice from 50% alcohol, separating slowly as purplish, lenticular, microscopic platelets, which contain 1.5 molecules of water of crystallization when air-dry and effervesce at 155–60°. The yield was 4.5 g. When rapidly heated to 155°, then slowly, the anhydrous arsonic acid softens at about 155–60° and melts and evolves gas at about 200–10°. It is appreciably soluble in methyl alcohol, and in dilute, as well as strong alcohol. It melts in boiling water, in which it is appreciably soluble, and separates on cooling as an emulsion. It is insoluble in hot acetone.

Subs., air-dry, 0.5600; loss, 0.0333, *in vacuo* at 100° over H₂SO₄.

Calc. for C₂₀H₁₉O₈N₂As.1.5H₂O: H₂O, 5.76. Found: 5.95.

Subs. anhydrous, 0.0917; 5.0 cc. N (20.8°, 756 mm.). Subs., 0.3040; Mg₂As₂O₇, 0.1056.

Calc. for C₂₀H₁₉O₈N₂As: N, 6.34; As, 16.96. Found: N, 6.31; As, 16.76.

N-(Phenyl-4-arsonic Acid)- α -phenylglycine-4'-uraminoanilide, *p*-H₂O₃AsC₆H₄NHCH(C₆H₅)CONHC₆H₄NHCONH₂(*p*).—The condensation of arsanilic acid and *p*-phenylchloroacetyl-aminophenyl-urea¹ (12.2 g.) was effected exactly as in the preceding example. Crystallization of the product, which started on cooling and scratching, was complete after 24 hours. After washing with 50% alcohol the substance was dissolved in dil. sodium hydroxide, the solution neutralized to litmus with acetic acid, filtered, diluted with hot water, and acidified with acetic acid. The arsonic acid separated as a gummy mass which gradually hardened and was then filtered off and washed with water. The yield was 11 g., decomposing after drying *in vacuo* at 100° at about 255° with preliminary darkening and softening. It dissolves in boiling 50% alcohol, but is very difficultly soluble in boiling water.

¹ THIS JOURNAL, 39, 1445 (1917).

Subs., 0.1414; 14.2 cc. N (23.0°, 764 mm.). Subs., 0.3575; Mg₂As₂O₇, 0.1134.

Calc. for C₂₁H₂₁O₆N₄As: N, 11.57; As, 15.49. Found: N, 11.65; As, 15.31.

N-(Phenyl-4-arsonic acid)- α -phenylglycine-3'-carbamidoanilide, *p*-H₂O₃AsC₆H₄NHCH(C₆H₅)CONHC₆H₄CONH₂(*m*).—5.9 g. of *m*-phenylchloroacetyl-aminobenzamide,¹ gradually yielded a clear solution. After 4 hours the arsonic acid separated on rubbing, and was washed with 50% alcohol. It was then suspended in water and ammonia added in excess, and the solution treated with bone black to remove the turbidity. The filtrate was diluted to large volume with hot water and acidified with acetic acid, whereupon the acid gradually separated on scratching in microcrystalline form and in a yield of 7 g. It darkens and softens slightly above 250°, melts with effervescence at 261–2°, and is practically insoluble in boiling water or 50% alcohol.

Subs., 0.1431; 11.3 cc. N (23.5°, 760 mm.). Subs., 0.3522; Mg₂As₂O₇, 0.1183.

Calc. for C₂₁H₂₀O₆N₃As: N, 8.96; As, 15.97. Found: N, 9.09; As, 16.20.

N-(Phenyl-4-arsonic Acid)- α -phenylglycyl-4-aminophenylacetamide, *p*-H₂O₃AsC₆H₄NHCH(C₆H₅)CONHC₆H₄CH₂CONH₂(*p*).—The reaction mixture, containing 6.1 g. of α -phenylchloroacetyl-*p*-aminophenylacetamide,¹ was boiled for 3 hours, quickly becoming clear. Dilution with several volumes of water caused the deposition of a thick oil which began to crystallize after a few days. The process was hastened by warming the mixture on the water bath and rubbing, after which the substance was filtered off hot and washed with hot water. The crude product was dissolved in very dilute ammonia, treated with bone black, and the filtrate warmed on the water bath and gradually treated with an excess of acetic acid, seeding at the same time with a crystal of the crude substance and rubbing with a rod. In this way partial separation as an oil was avoided. The yield was 6 g. The arsonic acid was recrystallized from 50% alcohol, forming minute plates and flat needles which contain 1/2 molecule of water of crystallization. When anhydrous it turns yellow and softens on heating, melting with decomposition at 222–3°. It is sparingly soluble in boiling water and somewhat more easily in boiling 50% alcohol.

Subs., air-dry, 0.5309; loss, 0.0086, *in vacuo* at 100° over H₂SO₄.

Calc. for C₂₂H₂₂O₆N₃As.0.5H₂O: H₂O, 1.62. Found: 1.82.

Subs., anhydrous, 0.1366; 10.3 cc. N (21.0°, 769 mm.). Subs., 0.3015; Mg₂As₂O₇, 0.0956.

Calc. for C₂₂H₂₂O₆N₃As: N, 8.70; As, 15.52. Found: N, 8.87; As, 15.30.

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¹ THIS JOURNAL, 39, 1445 (1917).